Reproductive Endocrinology and Infertility: *Clinical Expert Series*

Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is a highly prevalent disorder, representing the single most common endocrine–metabolic disorder in reproductive-aged women. Currently there are four recognized phenotypes of PCOS: 1) hyperandrogenism+oligo-anovulation+polycystic ovarian morphology; 2) hyperandrogenism+oligo-anovulation; 3) hyperandrogenism+polycystic ovarian morphology; and 4) oligo-anovulation+polycystic ovarian morphology, each with different long-term health and metabolic implications. Clinicians should clearly denote a patient's phenotype when making the diagnosis of PCOS. Polycystic ovary syndrome is a highly inherited complex polygenic, multifactorial disorder. Pathophysiologically abnormalities in gonadotropin secretion or action, ovarian folliculogenesis, steroidogenesis, insulin secretion or action, and adipose tissue function, among others, have been described in PCOS. Women with PCOS are at increased risk for glucose intolerance and type 2 diabetes mellitus; hepatic steatosis and metabolic syndrome; hypertension, dyslipidemia, vascular thrombosis, cerebrovascular accidents, and possibly cardiovascular events; subfertility and obstetric complications; endometrial atypia or carcinoma, and possibly ovarian malignancy; and mood and psychosexual disorders. The evaluation of patients suspected of having PCOS includes a thorough history and physical examination, assessment for the presence of hirsutism, ovarian ultrasonography, and hormonal testing to confirm hyperandrogenism and oligo-anovulation as needed and to exclude similar or mimicking disorders. Therapeutic decisions in PCOS depend on the patients' phenotype, concerns, and goals, and should focus on 1) suppressing and counteracting androgen secretion and action, 2) improving metabolic status, and 3) improving fertility. However, despite significant progress in understanding the pathophysiology and diagnosis of the disorder over the past 20 years, the disorder remains underdiagnosed and misunderstood by many practitioners.

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Polycystic ovary syndrome (PCOS) is a highly prevalent disorder, representing the single most common endocrine–metabolic disorder in reproductive-aged women. The first concrete medical report of PCOS in contemporary medical literature was the seminal account of Stein and Leventhal,[1] who were the first to describe a series of patients, rather than isolated cases, with the triad of polycystic ovaries, hirsutism, and oligo-amenorrhea, clinically linking what had previously been seemingly unrelated features. Yet, despite significant progress in understanding the pathophysiology and diagnosis of the disorder over the past 20 years, the disorder remains underdiagnosed and misunderstood by many practitioners.[2] More recently, there has been increasing interest in potentially renaming PCOS to better describe its endocrine–metabolic roots or recognize the different phenotypes of the disorder. Further, and regardless of

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what it should be called, it is clear that the clinician community needs to become better educated, knowledgeable, and more vigilant concerning this highly pervasive disorder. Following is a review the definition, clinical presentation, epidemiology, associated morbidities, genetics, pathophysiology, diagnosis, and treatment of PCOS.

DEFINITION

There are three diagnostic criteria for PCOS in use today[3] (Table 1). Although there are small differences in the diagnostic schemes of these criteria, they overall use the same features. Examination of the criteria indicates that two criteria (ie, those of the 2003 Rotterdam and the 2006 Androgen Excess & PCOS Society) represent expansions of the first (the 1990 National Institutes of Health criteria) (Table 1). The 1990 National Institutes of Health criteria define two phenotypes: phenotype A (hyperandrogenism+oligo-anovulation+polycystic ovarian morphology) and phenotype B (hyperandrogenism +oligo-anovulation, but not polycystic ovarian morphology). Phenotype A is often referred to as the "complete" PCOS phenotype, and both phenotypes A and B are often referred to as "classic" PCOS. The 2006 Androgen Excess & PCOS Society and the 2003 Rotterdam criteria include an additional phenotype, phenotype C (hyperandrogenism+polycystic ovarian morphology, but without oligo-anovulation), the so-called "ovulatory" PCOS. Finally, the 2003 Rotterdam criteria introduced a fourth PCOS phenotype, phenotype D (oligo-anovulation+polycystic ovarian morphology, without hyperandrogenism), often termed "nonhyperandrogenic" PCOS (Table 1). In 2012, a National Institutes of Health Consensus Conference Panel recommended that the 2003 Rotterdam be used but with the proviso that the specific PCOS phenotypes identified be noted.[4]

All definitions for PCOS mandate the systematic exclusion of similar or mimicking disorders. In patients with evidence of ovulatory dysfunction, other common causes of oligo-anovulation should be excluded such as thyroid dysfunction and hyperprolactinemia by measuring thyroid-stimulating hormone and prolactin, respectively (Box 1). In patients with evidence of androgen excess, 21-hydroxylase (an activity determined by P450c21 and encoded by *CYP21A2*) deficient nonclassic adrenal hyperplasia should be excluded by the measurement of a basal 17-hydroxyprogesterone level, obtained in the follicular (preovulatory) phase and preferably in the morning.[5] Patients with a screening 17-hydroxyprogesterone level greater than 2 ng/mL (200 ng/dL) should undergo an acute adrenocorticotropic hormone stimulation test (see Diagnosis–Hormonal Testing). Cushing's syndrome, androgen-secreting neoplasms, and disorders of severe insulin resistance (eg, so-called hyperandrogenic-insulin resistance-acanthosis nigricans [HAIRAN syndrome] or syndromes of lipodystrophy) should be excluded by appropriate tests if suspected clinically (Box 1 and below).

EPIDEMIOLOGY

The first study to establish the prevalence of PCOS in an unselected population was carried out in the

Table 1. The Diagnostic Criteria for Polycystic Ovary Syndrome

	1990 NIH	2003 ESHRE/ASRM (Rotterdam)	2006 AE-PCOS Society	2012 NIH Consensus[4]
Criteria	2 of 2 criteria required: 1. HA 2. OA	2 of 3 criteria required: 1. HA 2. OA 3. PCOM*	2 of 2 criteria required: 1. HA 2. Ovarian dysfunction (OA, PCOM, or both*)	Recommended use of the 2003 Rotterdam criteria, but with the specification that the specific phenotypes included be identified: • Phenotype A: HA+OA+PCOM* • Phenotype B: HA+OA • Phenotype C: HA+PCOM* • Phenotype D: OA+PCOM*
Exclusions	Exclusion of similar or mimicking disorders			

NIH, National Institutes of Health; ESHRE, European Society for Human Reproduction & Embryology; ASRM, American Society of Reproductive Medicine; AE-PCOS, Androgen Excess & PCOS; HA, clinical or biochemical hyperandrogenism or both; OA, oligo-anovulation; PCOM, polycystic ovarian morphology.

* PCOM is defined as at least one ovary with an ovarian volume of greater than 10 cm^3 (or 10 mL) or an increased antral follicle count (AFC), that is, those that can be visualized as cysts in the ovarian cortex measuring 2–9 mm in diameter, or both. Although older studies suggest that AFCs of 12 or greater (assessing the entirety of the ovary, not just a single cross-sectional slice) indicated PCOM, more recent studies suggest that the diagnostic AFC may be as high as 18. See text for more data.

Box 1. Hormonal Testing and Imaging in the Evaluation for Polycystic Ovary Syndrome

Hormonal testing

- Hormonal testing to detect or confirm hyperandrogenism:
  - Total and free T, principally in those patients with unclear evidence of clinical hyperandrogenism
  - DHEAS, A4, or both increases the detection of hyperandrogenemia by approximately 15–20%
- Hormonal testing to detect or confirm ovulatory dysfunction:
  - P4 day 22–24 of cycle to detect ovulation in eumenorrheic hirsute patients
  - AMH to assess for increased antral follicle count
- Hormonal testing to exclude similar or mimicking disorders:
  - TSH in all patients to exclude thyroid dysfunction
  - Prolactin in all patients to exclude hyperprolactinemia
  - Basal 17-hydroxyprogesterone in the follicular phase and morning in all patients to exclude 21-OH-deficient NCAH
  - Acute ACTH stimulation test as indicated by the results of the basal 17-hydroxyprogesterone to diagnose 21-OH-deficient NCAH
  - OGTT for insulin and glucose as clinically indicated to exclude syndromes of severe insulin resistance (HAIRAN syndrome or syndromes of lipodystrophy)
  - Twenty-four-hour urine free cortisol or cortisol after an overnight dexamethasone suppression test, as clinically indicated to exclude Cushing's syndrome

Imaging

- Pelvic ultrasonography in all patients to assess ovarian morphology, endometrial thickness, and other pelvic pathology
- Adrenal CT or MRI, as clinically indicated to exclude adrenal neoplasms
- Pituitary CT or MRI, as clinically indicated to exclude pituitary or sellar neoplasms

T, testosterone; DHEAS, dehydroepiandrosterone sulfate; P4, progesterone; AMH, anti-müllerian hormone; TSH, thyroid-stimulating hormone; 21-OH, 21-hydroxylase; NCAH, nonclassic adrenal hyperplasia; ACTH, adrenocorticotropic hormone; OGTT, oral glucose tolerance test; HAIRAN, hyperandrogenic-insulin resistance-acanthosis nigricans; CT, computed tomography; MRI, magnetic resonance imaging.

southern United States and published in 1998.[6] Since then, a number of studies have reported a prevalence of PCOS affecting between 5 and 20% (1/20 to 1/5) of reproductive-aged women, depending on the definition used.[7] Across most of these studies, and despite variations in methodology, the prevalence of PCOS defined by the 1990 National Institutes of Health criteria has been relatively uniform, between 5 and 10%, whereas the prevalence of PCOS by the 2006 Androgen Excess & PCOS Society definition ranges from 10–15% and that of PCOS per 2003 Rotterdam ranges from 5–20%.[8] Overall, the prevalence of PCOS in a population is not associated with the degree of obesity in that population,[8] suggesting that PCOS is not a consequence of the modern-day obesity epidemic.

CLINICAL PRESENTATION

Polycystic ovary syndrome is a clinical syndrome, that is, a collection of signs and symptoms, including clinical or biochemical hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology, which we define as follows.

Clinical Hyperandrogenism

The most common clinical sign of hyperandrogenism is hirsutism or the presence of excess terminal hairs in a male-like pattern. Terminal hairs refer to hairs that grow greater than 5 mm in length (if left uncut), are medullated (having a central core of compact keratinocytes), and often have both shape and pigment. Alternatively, vellus hairs are unmedullated, softer, generally less than 5 mm in length, may or may not be pigmented, and have uniform shape. Male-like pattern refers to hair growth in areas in which men generally develop terminal hair growth.

Clinically, the extent of terminal hair growth in male-like areas is assessed using a visual scale, the modified Ferriman-Gallwey score.[9] The modified Ferriman-Gallwey score is obtained by assigning a score of 0 (no visible terminal hairs) to 4 (terminal hair growth consistent with that of a normal male) for nine body areas (upper lip, chin and neck, upper chest, upper abdomen, lower abdomen or male escutcheon, upper back, lower back, upper arms, and thighs) and then summing the values (Fig. 1). A few caveats to assessing the modified Ferriman-Gallwey score should be considered (Box 2). A color atlas has been published to assist in assessing the modified Ferriman-Gallwey score reliably.[9]

The last part of the definition of hirsutism rests on the term "excess." What amount of terminal hair in male-like areas of the body of women is too much? Most observers note that scores greater than the 95th percentile of the population should be considered excessive, reporting cutoff modified Ferriman-Gallwey scores of 6, 7, 8, or even 10. However, there is little biological or medical reason to designate the upper fifth percentile of any population as abnormal.

To determine what is abnormal in terms of terminal hair growth in women, we carried out a large study in unselected black and white women.[10]

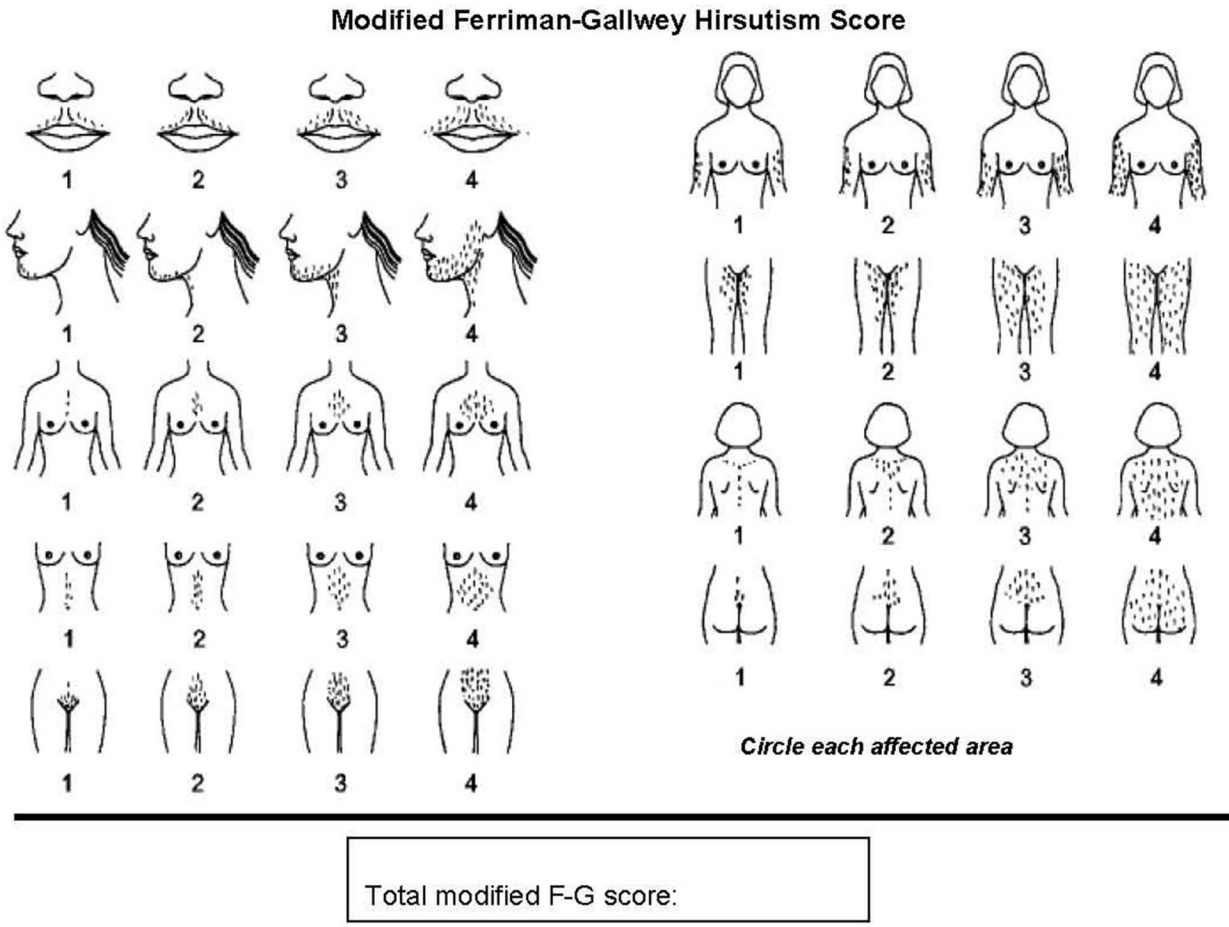

Fig. 1. The modified Ferriman-Gallwey (mFG) scoring system for hirsutism. See text for details. ©Copyright 2005 Ricardo Azziz, reproduced with permission.
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Using cluster analysis and associated symptoms, our data indicated that a modified Ferriman-Gallwey value of 3 or more defined abnormal. A study in Han Chinese found a comparable cutoff value using a similar approach.[11] Thus, although modified Ferriman-Gallwey scores of 6 or greater may be used to define significant hirsutism, scores of 3 or more will define abnormal terminal body or facial hair growth that should be evaluated. Consistent with this fact, in a separate study, Souter et al[12] found that more than 50% of women with minimal amounts of excess terminal hair growth (ie, modified Ferriman-Gallwey scores of 1–5) experienced a hyperandrogenic disorder. Consequently, even women with minimal degrees of excess body and face terminal hair growth, or even those who report being excessively hairy, should be evaluated for androgen excess. The degree of hirsutism is an indicator of the severity of metabolic dysfunction.[13]

Other clinical signs of hyperandrogenism include acne and alopecia. However, acne in the absence of hirsutism is at best an unreliable sign of androgen excess.[14] Likewise, the majority of women with female alopecia (diffuse and sagittal) do not have hyperandrogenism.[14]

Biochemical Hyperandrogenism

Hyperandrogenism can also be established by evidence of excess androgen concentrations in the circulation. However, the detection of hyperandrogenemia is not as straightforward as it may seem, and various caveats should be kept in mind (Box 3). Notable is the need to use the most sensitive and accurate assays possible, primarily mass spectrometry or high-quality immunoassays after extraction and chromatography.

Ovulatory Dysfunction

Oligo-ovulation is generally detected by the length of the menstrual cycle (ie, the time between vaginal bleeding episodes). Based on older epidemiologic data,[15] oligo-anovulation can be defined as menstrual cycles greater than 35 days in length, which in turn translates into 10 or less cycles per year. For greater rigor, some investigators prefer to use as a definition of oligo-anovulation eight cycles or less per year, which is the equivalent of cycles greater than 45 days in length. However, not all oligo-anovulation presents as clinically evident oligo-amenorrhea. In some women, ovulatory dysfunction will present as frequent menstrual bleeding (polymenorrhea), whereas other affected patients may present with apparent "regular" monthly cycles (ie, eumenorrhea).[16] In fact, up to 40% of hirsute women who claim to be eumenorrheic are oligo-anovulatory.[14] As for hirsutism,[13] the severity of the menstrual dysfunction directly correlates with the degree of insulin resistance.[16]

Polycystic Ovarian Morphology

Although polycystic ovarian morphology can be detected histopathologically, clinically most polycystic ovarian morphology is detected by transvaginal ultrasonography. Polycystic ovarian morphology is defined as at least one ovary with an ovarian volume of greater than 10 cm^3 (or 10 mL) or an increased number of antral follicles (ie, those that can be visualized as cysts in the ovarian cortex measuring 2–9 mm in diameter). The exact number of antral follicles, that is, the antral follicle count, to establish the diagnosis of polycystic ovarian morphology using modern high-frequency transvaginal ultrasonography probes is now at least 18 if not higher.[17] A few caveats in assessing polycystic ovarian morphology by ultrasonography are depicted in Box 4.

Although clinical symptoms are most pronounced in the reproductive years, the disorder does result in symptomatology and morbidity throughout the lifespan.[18] Before menarche, affected children may present with exaggerated or premature adrenarche (excess adrenal androgen production for age). Alternatively, in women as they approach their late reproductive years and into menopause, androgen biosynthesis progressively declines, and hirsutism and oligo-anovulation may improve clinically.

Finally, we must recognize that the clinical phenotype of PCOS reported by most investigators is primarily based on the evaluation of patients seen in the clinical setting. However, it is clear that there is significant referral bias in PCOS. Hence, patients seen in the clinical setting are often more severely hyperandrogenic and more obese than are women with PCOS detected in epidemiologic studies.[9]

Box 2. Caveats When Assessing for Hirsutism

- The entire body should be assessed.
- Patients should be assessed prior to hair removal.
- The degree of variability in assessing the mFG score should be minimized.
- The cutoff value defining what is a supranormal mFG is often quite low, 3 or greater.
- Women with minimal degrees of excess terminal hair growth or those who report being excessively hairy should be evaluated for androgen excess.
- Hyperandrogenism-related terminal hair growth will develop progressively and may often not be fully expressed in adolescents with PCOS.

mFG, modified Ferriman-Gallwey; PCOS, polycystic ovary syndrome.

ASSOCIATED FEATURES AND MORBIDITIES

Overweightness and Obesity

Excess adiposity has been associated with PCOS with various reports noting that between 30% and 60% of women with PCOS demonstrate obesity.[3] However, and as indicated previously, patients seen in the clinical setting are more obese and more hyperandrogenic (and in the United State more non-Hispanic white) than women with PCOS detected in medically unbiased (unselected) populations. In fact, the difference in the prevalence of obesity and overweightness is relatively modest, if any at all, between PCOS and unaffected women in the same population.[9] Furthermore, there appear to be little differences in the body distribution of adiposity between PCOS and body mass-matched control women.[19,20]

Metabolic Dysfunction

A majority of patients with PCOS demonstrate chronic insulin resistance beyond that dictated by body mass only.[21] However, despite their ability to produce excess insulin in the face of insulin resistance, patients with PCOS produce less insulin than would be determined by their degree of insulin resistance, suggesting a relative degree of β cell dysfunction. As a result of their insulin resistance and suboptimal compensatory hyperinsulinemia, patients with PCOS are at increased risk for impaired glucose tolerance and type 2 diabetes mellitus. In fact, patients with PCOS are five- to sevenfold more likely to have type 2 diabetes mellitus than age-matched control women.[22] Additionally, they are at increased risk for metabolic syndrome, a complex of signs and symptoms that

Box 3. Caveats to Assessing for Biochemical Hyperandrogenism

- At least one abnormal androgen value is required to diagnose hyperandrogenemia.
- Total and free T should always be assessed.
  - DHEAS and A4 assessment are optional and may identify an additional 15–20% of women as being hyperandrogenemic.
- The quality, specificity, and sensitivity of the assays are critical.
  - Total T should be assayed using either a high-quality RIA after sample extraction and column chromatography or mass spectrometry after sample extraction.
  - Free T should be assessed using equilibrium dialysis, ultrafiltration, or ammonium sulfate precipitation or presented as the ratio of total T to SHBG (ie, the FAI).
- Normative ranges should be developed using either well-defined "super-controls" or cluster analysis in a larger population.
- Cutoff values selected for androgen assays should consider the background frequency of the disorder.
- Androgen levels vary with age and many (eg, DHEAS) require the use of age-dependent normative ranges.
- In patients who are already hirsute, the measurement of circulating androgen adds little to their evaluation.
- Androgen levels, in contrast to clinical presentation, are poor predictors of androgen-secreting neoplasms.
- In most adolescents, androgen levels usually will be within the adult range after age 14 years.

T, testosterone; DHEAS, dehydroepiandrosterone sulfate; RIA, radioimmunoassay; SHBG, sex hormone-binding globulin; FAI, free androgen index.

increase the risk for cardiovascular disease and type 2 diabetes mellitus. Overall, the prevalence of metabolic syndrome in PCOS, depending on how defined, appears to be twice as high in PCOS as in women of similar age and body mass without the disorder.[22] Additionally, patients with PCOS are at higher risk for macrovascular hepatic steatosis, also termed nonalcoholic fatty liver disease.[22] Nonalcoholic fatty liver disease, if left untreated, can result in abnormal liver function, steatohepatitis, cirrhosis, and, rarely, hepatocellular carcinoma.

Vascular Dysfunction

The prevalent insulin resistance, hyperinsulinemia, and chronic subacute inflammation result in an increased risk for abnormal vascular function. Consequently, patients with PCOS are at greater risk for hypertension, cerebrovascular accidents, and deep vein thrombosis.[22] Alternatively, although women with PCOS demonstrate dysfunction of their coronary vasculature, few data have been able to demonstrate an increased incidence of, or risk for, cardiovascular events (eg, myocardial infarction).[23,24] Whether PCOS is somehow protective against cardiovascular events, in the face of other risk factors, is still unclear.

Malignancy

The combination of oligo-anovulation and hyperinsulinemia places patients with PCOS at increased risk for endometrial hyperplasia and carcinoma.[22] Consequently, endometrial biopsies should be considered liberally in patients with PCOS with a long-term history of untreated oligo-anovulation, particularly if endometrial thickness on ultrasonography is increased. Patients with PCOS may also be at increased risk for ovarian, but not breast, cancer.[22]

Reproductive Complications

Most patients with PCOS experience oligo-anovulation, which results in subfertility associated with ovulatory dysfunction.[22] Once they conceive, women with PCOS do not appear to demonstrate an increased risk for miscarriages or early pregnancy loss, although they do seem to be at increased risk for various obstetric complications including pregnancy-induced hypertension, gestational diabetes mellitus, and macrosomia.[22,25]

Mood Disorders and Quality of Life

Women with PCOS are at greater risk for anxiety and depression, whose risk appears to be most strongly correlated to the patients' androgen excess and hyperinsulinism.[22,26] Other potential contributors might include the chronic and complex nature of the condition and poor diagnostic experience. Not surprisingly, patients with PCOS demonstrate reduced quality of life, most strongly determined by the presence of hirsutism and obesity, two factors that detrimentally affect an individual's self-esteem and body image, and by the presence of a concomitant mood disorder.[22]

GENETICS AND EVOLUTION

Polycystic ovary syndrome is a highly inherited complex polygenic, multifactorial disorder. Numerous candidate genes have been studied, largely through association studies, using a candidate gene approach, transmission disequilibrium test (family-based association), or genome-wide association study. Of note, genome-wide association studies

Box 4. Caveats When Assessing for Polycystic Ovarian Morphology

- Most women with PCOS will have PCOM if assessed carefully.
- If ultrasonography has to be performed transabdominally, ovarian volume may be a better predictor than antral follicle count for the diagnosis of PCOM.
- The presence of a concomitant ovarian follicle greater than 1 cm (10 mm) may suggest imminent ovulation, a process that in turn may disrupt the morphologic pattern of the ovary and the ultrasonogram should be repeated at a later date.
- PCOM may be variably suppressed (but not stimulated) by hormonal contraceptives; patients should preferably be scanned off hormonal suppression for at least 6 months.
- The frequency of PCOM-like findings in the ovaries, in the absence of any other sign or symptom of PCOS, is much higher than the prevalence of PCOS, and the sole presence of PCOM should not be regarded as indicative of PCOS.
- Many adolescents will demonstrate a PCOM-like morphology, and ovarian morphology should not generally be used to assess for PCOS in adolescents.

PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome.

identify loci (regions on chromosomes) that are of interest, not specific genes. Candidate genes suggested by a genome-wide association study have been found to be related to gonadotropin action, ovarian follicle development, insulin action, and organ growth,[27] including *FSHB* (follicle-stimulating hormone β subunit gene), *FSHR* (follicle-stimulating hormone receptor gene), *LHCGR* (luteinizing hormone [LH] choriogonadotropin receptor gene), *THADA* (THyroid ADenoma-Associated protein gene), *ERBB4* (Erb-B2 receptor tyrosine kinase 4 gene, also known as *HER4*), *GATA4*, *NEIL2*, *FDFT1*, *DENND1A* (the domain differentially expressed in normal and neoplastic domain containing 1A gene), *RAB5B, SUOX, HMGA2,* and *INSR* (insulin receptor gene).

It is important to note that although some of the loci identified do appear to be linked to the underlying biology of PCOS, linking the variants identified so far to functional abnormalities in PCOS is only just beginning. Furthermore, although the heritability of PCOS estimated in a monozygotic twin study is approximately 70%,[28] the proportion of heritability accounted for by the PCOS loci identified so far by an genome-wide association study is less than 10%, although this is no different than for other complex genetic traits.

Finally, similar variants have been described in Han Chinese and in European-descent populations,[29] suggesting that the disorder is probably at least 60,000 years old. Polycystic ovary syndrome represents an apparent evolutionary paradox, a disorder that results in subfertility (an evolutionary disadvantage) and yet appears to have persisted for millennia, has a relatively similar prevalence across the globe (in those populations studied so far), and affects up to one fifth of all humans. Although it is possible that PCOS provided some evolutionary advantage to ancient women and their communities, it is more likely that PCOS evolution has been driven by nonadaptive evolutionary mechanisms, including genetic drift resulting from a serial founder effect and population balance resulting from sexually antagonistic selection.[30]

PATHOPHYSIOLOGY

Although a thorough discussion of this complex topic exceeds the limits of this review, there are a number of generalities about the pathophysiology of PCOS that can be addressed, focusing on major defects observed and their interactions (Fig. 2).

At the hypothalamic–pituitary level, patients with PCOS demonstrate gonadotropin secretory abnormalities, including increased LH pulse amplitude and frequency, and increased circulating levels of LH, most evident in patients who are not obese. In addition, the hypothalamic–pituitary axis appears to be somewhat resistant to the suppressive effects of progesterone on gonadotropin-releasing hormone pulse frequency.[31] Increased LH pulses and enhanced daytime LH pulse secretion are observed early during puberty in girls with hyperandrogenism indicating that abnormalities in the release of gonadotropin-releasing hormone might be a primary defect in PCOS, at least in some patients. The increased LH levels serve to stimulate androgen secretion by the ovarian theca cells.

At the ovarian level, follicles demonstrate relative resistance to the follicle-stimulating hormone, which in part may be intrinsic to the disorder. However, it also may be secondary to the high levels of anti-müllerian hormone being secreted by the larger cohort of preantral follicles and the androgenic environment within the ovaries.[31] Other factors may also contribute to the abnormal follicular development of PCOS, including the elevated levels of circulating insulin and dysregulation of intraovarian factors modulating follicular recruitment and growth, including members of the transforming growth factor-β family (eg, anti-müllerian hormone, inhibins, activins, bone

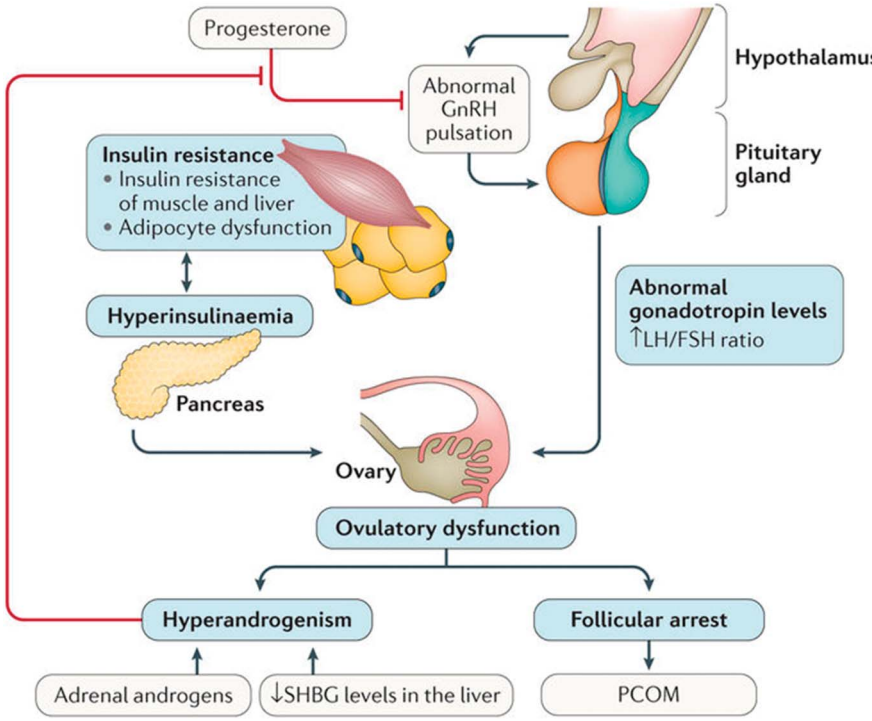

Fig. 2. The pathophysiology of PCOS. The pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus is often disturbed in polycystic ovary syndrome (PCOS), leading to luteinizing hormone (LH) hypersecretion by the pituitary gland, which induces ovulary dysfunction and hyperandrogenism. This perturbed secretion of LH seems to arise early in puberty and is related to disturbed inhibition of GnRH secretion by progesterone. Although serum follicle-stimulating hormone (FSH) levels are generally normal, follicles seem to be more resistant to FSH in women with PCOS than in control women. This effect might be the result of increased levels of intraovarian anti-Müllerian hormone (AMH). Notably, genetic and epigenetic variants contribute considerably to susceptibly for most of these alterations. Environmental factors contribute somewhat less, most by exacerbating insulin resistance and dysregulated gonadotropin secretion. PCOM, polycystic ovarian morphology; SHBG, sex hormone-binding globulin. Reprinted by permission from Springer Nature. Nat Rev Dis Primers 2016;2:16057. Polycystic ovary syndrome, Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, et al. Copyright 2016.

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morphogenic proteins, and growth differentiation factors), other growth factors, and cytokines.

There is also evidence of adrenocortical steroidogenic dysfunction in PCOS[31] with approximately one third of women with PCOS demonstrating excess dehydroepiandrosterone sulfate, an androgen metabolite or prohormone that is secreted almost exclusively by the adrenal cortex. However, the role of adrenal androgens in the development and maintenance of PCOS is still unclear.

The aforementioned insulin resistance and compensatory hyperinsulinemia play a critical role in the pathophysiology of PCOS. Excess insulin, acting synergistically with LH, stimulates androgen production by ovarian theca cells[32] and, along with androgen excess, suppresses the hepatic production of sex hormone-binding globulin.[33] Both of these factors favor the development of hyperandrogenism.

The etiology of the decreased insulin sensitivity in PCOS remains unclear, although the various genetic and epigenetic dysfunctions all appear to lead to defects in the production and action of the principal cellular transporter for glucose, glucose transporter 4 (GLUT4), and defects in insulin-mediated glucose disposal. Defects in insulin-mediated lipolysis are also evident in patients with PCOS. In addition, the degree of insulin resistance in PCOS is made worse by a state of chronic subacute inflammation, in part driven by abnormal adipocytokine production and action.[31]

Finally, the contribution of obesity and adipose distribution to the development of PCOS independent of its effect on insulin sensitivity is unclear and probably modest at best, especially when patients identified in medically unbiased settings are studied.[9] Alternatively, there is greater evidence that the adipose tissue of women with PCOS demonstrates various defects favoring an inflammatory or insulin resistant state, including adipocytokine dysfunction, free fatty acid metabolism dysregulation, and epigenetic abnormalities affecting GLUT4 function.[31]

Box 5. Therapeutic Options in Polycystic Ovary Syndrome

- Suppression of androgen production:
  - OCs
  - Other combination contraceptives (modest effect)
  - Progestin-only long-acting contraceptives (modest effect)
  - Metformin (modest effect)*
  - Dexamethasone or prednisone (for select NCAH only)
  - Long-acting GnRH analogs (for select severe hyperinsulinemia only)*
  - Ketoconazole (for select androgen-secreting neoplasms only)*
- For hirsutism:
  - Suppression of androgen production, particularly with OCs
  - Androgen receptor blockers:
    - Spironolactone*
    - Flutamide*†
  - 5α-reductase inhibition
    - Finasteride*
  - Hair follicle ornithine decarboxylase inhibition
    - Topical eflornithine HCL, 13.9% solution
  - Cosmetic therapies
    - Shaving, depilation, bleaching
    - Electrology
    - Laser epilation
- For androgen-related acne:‡
  - Suppression of androgen production, particularly with OCs (see above)
  - Topical treatments (eg, benzoyl peroxide, antibacterials, astringents)
  - Oral antibiotics
  - Oral isotretinoin
- For androgen-related alopecia:
  - Suppression of androgen production, particularly with OCs (see above)
  - Finasteride§
  - Topical minoxidil, 2% and 5% solution
  - Hair transplantation
- Protection of endometrium and amelioration of menstrual dysfunction
  - OCs
  - Other combination contraceptives
  - Progestin-only long-acting contraceptives
  - Progestin-releasing intrauterine devices
  - Metformin (modest effect)*
- Improvement of metabolic status and potential amelioration of long-term metabolic risks‖
  - Lifestyle modification (in obese patients)
  - Metformin (modest effect)
  - Thiazolidinediones (for severe insulin resistance)
  - Bariatric surgery
- Ovulation induction (for anovulatory fertility)
  - Lifestyle modification (in obese women)
  - Clomiphene citrate
  - Letrozole*
  - Metformin (modest effect)*
  - Laparoscopic ovarian drilling or wedge resection
  - Recombinant FSH
  - Human menopausal gonadotropins

OCs, oral contraceptives; NCAH, nonclassic adrenal hyperplasia; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone.

*Not approved for this purpose by the U.S. Food and Drug Administration.

†Associated with rare, but severe and possibly fatal, hepatotoxicity.

‡Antiandrogens work poorly in androgen-related acne.

§Androgen receptor blockers have limited effect in androgen-related alopecia.

‖If other metabolic dysfunctions are present, additional therapies should be considered such as statins for dyslipidemia.

DIAGNOSIS

The most critical factor in the diagnosis of PCOS is physician awareness, knowledge, and attentiveness to the possibility of the diagnosis. One third or more of women reported greater than 2 years and three or greater health professionals before a diagnosis was established.[34]

Overall, two features can generally be used to identify patients at higher risk for PCOS: 1) women who report, or have clinical evidence of, excess male-like body or facial hair; and 2) women with a history of menstrual irregularity or oligo-amenorrhea. Subsequently, the diagnosis of PCOS is based on assessment of their hyperandrogenic status, ovulatory function, and ovarian morphology and the exclusion of related or mimicking disorders.

The broadest possible population for those practitioners most interested in the reproductive morbidities of PCOS will be identified using the Rotterdam 2003 criteria (Table 1). However, regardless of which criteria are selected for diagnosis, clinicians should be clear that they should also define which phenotype (A–D) the patient has, because each is associated with a different risk for metabolic and other morbidities. Following we detail the evaluation of the patient suspected of having PCOS.

History and Physical

First, all patients being evaluated for PCOS should undergo a complete medical history with a focus on sign and symptom initiation and progression, family history, response to treatment, whether intended or not, concomitant conditions or therapies, and current complaints. The physical examination should include a full body assessment for evidence of excess terminal hair growth, alopecia, acne, acanthosis nigricans, obesity and adiposity distribution, virilization or masculinization (severe hirsutism, clitoromegaly), thyroid shape and texture, and Cushingoid features.

Ovarian and Pelvic Ultrasonography

As indicated before, an ultrasonogram of the pelvis, preferably a transvaginal ultrasonogram, should be performed to assess the volume and antral follicle count of each ovary.

Hormonal Testing

Assessment of circulating hormones in patients with suspected PCOS is carried out for three purposes: 1) to confirm or demonstrate hyperandrogenism, 2) to confirm or demonstrate ovarian dysfunction, and 3) to exclude similar or mimicking disorders (Box 1). Of note, detection of hyperandrogenemia is most valuable in those patients without clear clinical evidence of hyperandrogenism; if androgen measures are to be used for the evaluation of a patient with suspected PCOS, the assays used must be of the greatest quality and sensitivity. Also as indicated previously, up to 40% of eumenorrheic hirsute patients have oligo-anovulation when assessed carefully.[14] The simplest way to evaluate for oligo-anovulation in these patients is to obtain a progesterone level on days 22–24 of the cycle (a bit later than usual for ovulation monitoring to detect late ovulations), preferably in more than one cycle (Box 1).

In addition, various investigators have suggested using anti-müllerian hormone instead of transvaginal ultrasonography to assess ovarian status such that elevated anti-müllerian hormone reflects the presence of an increased number of preantral follicles.[31] However, current data suggest that the use of anti-müllerian hormone for the diagnosis of PCOS still requires consideration of an ovarian transvaginal ultrasonography.[35] Further studies are also required to determine optimum anti-müllerian hormone assay characteristics, cutoff values, and predictive power of anti-müllerian hormone in the diagnosis of PCOS.

Although most similar or mimicking disorders are excluded by the clinical evaluation, some of these need to be excluded or diagnosed by more specific hormonal testing. Principal among these are thyroid disorders, hyperprolactinemia, and nonclassic adrenal hyperplasia, excluded by the measurement of thyroid-stimulating hormone, prolactin, and 17-hydroxyprogesterone, respectively.

Nonclassic adrenal hyperplasia resulting from defects in *CYP21A2* affects between 1 and 10% of hirsute women, depending on ethnicity, and is the single most common autosomal-recessive disorder of humanity. Although the American College of Obstetricians and Gynecologists' 2018 Practice Bulletin on PCOS recommends screening for nonclassic adrenal hyperplasia with 17-hydroxyprogesterone only in those women who are members of groups at higher risk for nonclassic adrenal hyperplasia,[36] other data suggest that early diagnosis and corticosteroid treatment may improve reproductive outcome.[37] Hence, all women with hyperandrogenic signs, symptoms, or complaints, regardless of degree, should be screened for nonclassic adrenal hyperplasia. Practitioners should note

that it is not possible to diagnose or even assume the diagnosis of nonclassic adrenal hyperplasia clinically[38] and assessment of 17-hydroxyprogesterone is mandatory.

Screening for nonclassic adrenal hyperplasia can be performed using a basal follicular phase (preferably morning) 17-hydroxyprogesterone.[5] If the screening value exceeds 2 ng/mL (200 ng/dL), patients should undergo an acute adrenocorticotropic hormone-1-24 stimulation test with 17-hydroxyprogesterone measured before (to ensure response) and 30–90 minutes after. Poststimulation levels of 17-hydroxyprogesterone greater than 10 ng/mL (1,000 ng/dL) generally indicate nonclassic adrenal hyperplasia (although occasionally a heterozygote for a *CYP21A2* mutation will exhibit this level of abnormality), whereas levels above 15 ng/mL (1,500 ng/dL or greater) almost certainly indicate nonclassic adrenal hyperplasia. Although genetic assessment of *CYP21A2* can be used to confirm the diagnosis as well as assess the type of defect carried, it should not be used to screen for nonclassic adrenal hyperplasia.

Finally, although hypothetically defects of *HSD3B2* and *CYP11B1*, determining 3β-hydroxysteroid dehydrogenase and 11β-hydroxylase activities, respectively, can result in nonclassic adrenal hyperplasia, few nonadolescent patients with these defects have been described and fewer still in the absence of genital ambiguity.[39,40] Thus, and contrary to 21-hydroxylase-deficient nonclassic adrenal hyperplasia, the routine screening for 3β-hydroxysteroid dehydrogenase and 11-hydroxylase-deficient nonclassic adrenal hyperplasia is not recommended.

Other Testing

The need for other hormonal testing (eg, 24-hour urine for free cortisol or overnight dexamethasone suppression test) and imaging (eg, of the adrenal) will be dictated by the clinical presentation (Box 1).

Assessment for Comorbidities

Once the diagnosis of PCOS is made (or during if the diagnosis appears nearly certain), assessment for metabolic status and comorbidities should be made. Impaired glucose tolerance and type 2 diabetes mellitus should be excluded by a 2-hour, 75-g oral glucose tolerance test (OGTT),[41] because basal glucose and glycosylated hemoglobin levels often fail to detect these in women with PCOS. The majority of women with PCOS with impaired glucose tolerance and approximately one third of those with type 2 diabetes mellitus will not be detected by a fasting glucose,[41] and glycosylated hemoglobin is not a predictable marker of glucose intolerance in PCOS when compared with an OGTT.[42] Including measurement of insulin during the OGTT can also provide additional evidence of the presence and degree of hyperinsulinemia, which basal insulin levels fail to identify. A lipid profile may also be obtained, regardless of age, as well as liver function tests in patients with obesity or marked hyperinsulinism. Repeat assessments of glucose tolerance and lipidemia should be performed every 2–3 years, unless there is a significant change in the clinical course.[41,43]

The transvaginal ultrasonogram used for the evaluation of ovarian morphology can also screen for other pelvic pathologies, including endometrial abnormalities. Furthermore, obese patients with PCOS may have sleep apnea, although it is not yet clear whether the incidence is greater than would be expected by weight alone.[44] Consequently, screening for sleep apnea should be performed using designated questionnaires or referral to a sleep specialist. Additionally, all patients with PCOS should be screened for mood disorders, either by the use of specific questionnaires or by referral to a specialist.[45]

Diagnosis in Adolescents

Many adolescents will demonstrate the full phenotype of PCOS at initial presentation, which facilitates the diagnosis. However, although circulating androgen levels reach adult levels generally by age 15 years (Box 3), the development of hirsutism may not reach adult standards until much later (Box 2). In addition, a multicystic ovarian morphology and oligo-anovulation may be more frequent in adolescent girls, independent of PCOS; in fact, ovarian morphology should not be used for the diagnosis of PCOS in this age group (Box 4). Consequently, it is critical that the diagnosis of PCOS not be rushed in young patients lest the patient is labeled (and treated) with a diagnosis that she does not have,[46] a label that has lifelong implications. Close (but not overzealous) follow-up and evaluation are recommended in adolescents whose diagnosis is yet unclear.

THERAPY

The selection of therapeutic agents in PCOS depends on the patients' phenotype, concerns, and goals. Therapy in PCOS will be focused on 1) suppressing and counteracting androgen secretion and action, 2) protecting the endometrium and improving menstrual dysfunction, 3) improving metabolic status, and 4)

improving ovulatory fertility. For example, hirsutism will respond to androgen suppression and androgen action blockade, whereas acne generally responds well solely to the suppression of androgen. Alternatively, female androgenic alopecia responds poorly to most therapies, albeit better to 5α-reductase than androgen receptor blockers. See Box 5 and also the report by Lizneva et al.[14]

A few caveats should be mentioned. In those patients who are not pursuing conception and in whom hormonal contraception is not contraindicated, treatment with combination oral contraceptives should be part of the initial therapy. Combination oral contraceptives suppress gonadotropin secretion and ovarian androgen production, regulate vaginal bleeding, and protect the endometrium. Although oral contraceptives may increase the degree of insulin resistance, they do so modestly.[47] Some patients may experience deep vein thromboses and other thrombotic events while on oral contraceptives, although it is unclear whether the risk is higher in PCOS than in any other patients of similar body mass on oral contraceptives.[47]

In patients who do not tolerate oral contraceptives, consideration may be given to transdermal combination contraceptives or progestin-only contraceptives. Alternatively, some patients may opt for cyclic progestogen administration, which will protect the endometrium and minimize the risk of endometrial hyperplasia, but not suppress androgen production. Suppression of ovarian androgen production by a long-acting gonadotropin-releasing hormone analog may be necessary on occasion, especially in the rare patient with extraordinarily high insulin levels (eg, hyperandrogenic-insulin resistant-acanthosis nigricans syndrome).[48] Patients may also experience reductions in circulating androgens secondary to weight loss or insulin sensitizer therapy (see "Improving Metabolic Status").

Counteracting Androgen Action

For patients with significant hirsutism, the addition of antiandrogens, including androgen receptor blockers such as spironolactone and flutamide, and 5α-reductase inhibitors such as finasteride will be of value.[14] Spironolactone (50–200 mg per day) is the preferred first-line agent, and although risks are few, some degree of side effects occur in more than 50% of patients taking spironolactone, most notably polyuria, hypotension, and syncope; salt-craving; dyspepsia; sensitivity to sun; and rarely atopic reactions. However, few patients discontinue the medication.[49]

In patients who do not tolerate spironolactone, 125–500 mg daily of flutamide may be considered. Because flutamide has been associated with rare acute hepatotoxic failure and death, it should be used sparingly and liver function tests assessed before and every 2–3 months during treatment. Cyproterone acetate, not available in the United States, is a progestogen with significant androgen receptor-blocking properties. It is usually available in a 2-mg dose in a combination oral contraceptive, although its antiandrogenic properties may not be readily perceived unless doses of 10–20 mg per day are used. Finally, 5 mg finasteride daily may be used to decrease hirsutism.

All antiandrogens share common risks and effects, including potential modest decreases in libido and muscular strength. They also have significant teratogenic potential for the feminization of a male fetus. Consequently, antiandrogens should not be administered without appropriate and secure contraception.

Because 5α-reductase inhibitors and androgen receptor blockers operate through different molecular mechanisms, it is possible to combine these medications for a synergistic effect. Likewise, antiandrogens may be combined with oral contraceptives for increased effect; oral contraceptives will also provide the necessary contraception for patients receiving antiandrogens. The response of hirsutism will often become apparent at 6 months of therapy, although frequently sooner.[49] Treatment should be continued for at least 2 years and then the dosage decreased or discontinued. Experience demonstrates that approximately 50% of patients in whom the medications are discontinued will need to restart suppression.

The topical application of a 13.9% solution of eflornithine hydrochloride may be of value for mild to moderate facial hair growth, regardless of etiology.[14] Eflornithine inhibits the activity of the enzyme ornithine decarboxylase, which plays a critical role in stimulating the growth of hairs, whether androgen-dependent or not. Eflornithine can be used in combination with other agents such as oral contraceptives and antiandrogens.

Improving Metabolic Status

For overweight or obese patients with PCOS, lifestyle modification, including weight loss, dietary adjustment, and increased exercise, should be part of their first-line therapy.[50] In some morbidly obese patients, or those obese patients with comorbidities, surgical means of weight reduction (eg, gastroplasty)

may be considered.[51] As with other obese individuals, women with PCOS respond well to caloric restriction.[50] Although there is no definitive study regarding which type of diet is best for the patient with PCOS, smaller studies and clinical experience suggest that diets lower in simple carbohydrates and sugars are preferred.[52] Weight loss in obese patients with PCOS is associated with modest improvements in menstrual and ovulatory function and hyperandrogenemia, albeit with significant improvements in metabolic status.[50]

The use of insulin sensitizers, particularly metformin (2,000–2,500 mg per day), should also be considered in metabolically challenged patients.[31,53] Although long-term prospective data are still lacking, therapy with metformin should be implemented on a long-term basis, unless significant changes in body habitus (ie, weight loss) occur. Patients on metformin may also experience small improvements in menstrual and ovulatory function and modest degrees of weight loss. Although not all women with PCOS will benefit from metformin, patients in whom the drug should be considered include those with elevated levels of insulin at baseline or during an OGTT, glucose intolerance, acanthosis nigricans, or a strong family history of diabetes.

Side effects of metformin include gastrointestinal distress and, very rarely, lactic acidosis. Administering the medication in divided doses, building up to the full dose over time, and using the extended-release formulation may all help reduce the incidence of significant gastrointestinal upset. Metformin is generally safe in pregnancy, if needed. Finally, other insulin sensitizers may be considered, including thiazolidinediones (eg, pioglitazone and rosiglitazone), although they should generally be reserved for patients with significant insulin resistance or glucose intolerance.

Managing Anovulatory Subfertility

For those patients desiring immediate fertility, treatment with an oral ovulatory agent (clomiphene citrate or letrozole) should be considered.[54] Approximately 50% of patients who ovulate on clomiphene will conceive after three to five cycles of treatment. Head-to-head studies have also suggested that letrozole is more effective than clomiphene,[55] but the U.S. Food and Drug Administration has not yet approved the former drug for the treatment of the infertile patient. Although the addition of metformin may improve the success of clomiphene a small amount, metformin should not be used as first-line agent for the ovulation induction of infertile patients with PCOS, because it is much less effective than clomiphene.[56]

In patients who fail to either ovulate or conceive on clomiphene or letrozole, gonadotropin ovulation induction or laparoscopic ovarian drilling can be considered.[57] Laparoscopic ovarian drilling can result in a spontaneous pregnancy or improve the response to oral ovulatory agents and in some cases provide longer term improvements in hyperandrogenemia and ovulation with a lesser risk for ovarian hyperstimulation syndrome and multiple births than gonadotropin ovulation induction. Alternatively, laparoscopic ovarian drilling is associated with the small risks of a surgical procedure, including premature ovarian failure, and periovarian adhesions. Finally, patients with PCOS who fail ovulation induction, or prefer not to proceed to either laparoscopic ovarian drilling or gonadotropin treatment, can choose to proceed to in vitro fertilization and embryo transfer. Patients with PCOS are at greater risk for ovarian hyperstimulation syndrome with gonadotropin ovulation induction and in vitro fertilization–embryo transfer and at higher risk for multiple pregnancies with gonadotropins.[58]

Cosmetic and Topical Treatments

For many patients with hirsutism and other dermatologic manifestations of hyperandrogenism, cosmetic or topical therapies should be considered and encouraged.[14] For hirsutism, in addition to the suppression of androgen secretion and action, cosmetic options may include bleaching (if mild), shaving and chemical epilation (if moderate), or shaving (if severe). In general, plucking in any form should be discouraged, because this action not only can damage the hair follicle canal, resulting in persistent folliculitis and ingrown hairs, but also stimulate further hair growth[59]; alternatively, shaving does not stimulate further hair growth.[60]

Permanent destruction of offending hair follicles can be achieved using electrology. Electrology usually uses a combination of thermal and galvanic energy transmitted through a fine needle placed down the hair follicle canal to destroy the hair follicle bulb. Although prospective studies are not available, experience indicates that in capable hands, electrology can achieve the permanent destruction of the intended hairs. The process is unfortunately slow and time-consuming (because the destruction is carried out hair follicle by hair follicle). Electrology should be used in combination with, and after sufficient time of,

hormonal suppression. Laser epilation has also been proposed and may achieve more rapid responses, although often with less permanency than electrology.[14]

A number of topical treatments for acne are available, including astringents, antibiotics, and retinoids. For androgenic alopecia, topical treatment with 2–5% topical minoxidil may be an option as may be topical finasteride. Hair transplant surgery may also be required. Long-term management of acne and alopecia would be best if carried out in consultation with a dermatologic expert.

Lifelong Therapy

Suppressive or maintenance treatment in PCOS generally implies lifelong follow-up and polytherapy involving a variety of therapeutic approaches, depending on presentation, comorbidities, age and life stage, family history, patient desires, and medical goals.

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